DETAILED ACTION

1. Applicant's amendment, filed 07/18/2011, has been entered.

Claims 20 and 51 have been amended.

Claims 1-11, 15-18, 20-21, 45-51 and 59-60 are pending.

Claims 12-14, 19, 22-44 and 52-58 have been canceled previously.

Applicant's election without traverse of Group I, drawn to methods of treating asthma with anti-C5 antibodies, filed 11/13/2006, has been acknowledged (e.g., see Office Action, mailed 03/13/2007).

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Office Action will be in response to applicant's arguments, filed 07/18/2011.

The rejections of record can be found in the previous Office Action, mailed 04/18/2011.

3. Priority.

As indicated previously, the effective filing date of the instant claims 1-11, 12-18, 45-50 and 59-60 appear to be the filing date of the priority application USSN 60/408,571, filed 09/06/2002.

Claims 20 and 51 do not have an effective priority date back to priority application USSN 60/408,571, filed 09/06/2002.

Applicant's arguments in conjunction with the Wang declaration under 37 C.F.R. § 1.131 filed 07/18/2011 have been fully considered but are not found convincing essentially for the reasons of record.

The Wang Declaration

As noted previously and in contrast to applicant's / declarant's assertions
and in contrast to applicant's assertion the examiner's position simply cannot stand under the weight of the objective reading of the Declaration in conjunction with the common scientific knowledge in the art on or around 12/20/2001,
the Wang 131 declaration does not provide for the generic anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b, as currently claimed.

With respect to applicant's reliance on upon Exhibits A/B to indicate that the inventor consistently referred to an anti-C5 antibody rather than the specific BB5.1 antibody,

the following is noted.

The purpose of the experimental plan for the asthma study clearly indicates "anti-C5(BB5.1)".

In turn, it is reasonably to conclude that the anti-C5 described in the Plan one refers back to BB5.1.

Note, too, that Plan two simply indicates BB5.1, rather than anti-C5.

Also, note, that Wang 131 Declaration in conjunction with Exhibits A/B refer to anti-C5 antibody and not an anti-C5 antibody that inhibits the conversion of complement component C5 into C5a and C5b as currently claimed.

In contrast to applicant's / counsel's assertions that the skilled artisan would have readily and unambiguously appreciated that anti-C5 and/or anti-C5 were terms of art referring to a genus of antibodies that inhibit the cleavage of C5 into fragments of C5a and C5b as instantly claimed,

including reliance upon Wang et al. (PNAS 92: 8955-8959, 1995) (1449; #CK1) and WO 95/29697 (1449)

that the artisan would have appreciated that the instant had conceived of the therapeutic use of antagonist anti-C5 antibodies by at least 12/20/2001 and had diligently carried out and completed the experiments described in the Declaration, as evidenced by priority USSN 60/408,571,

the following is noted.

Neither priority USSN 60/408,571, USSN 60/469,189 nor instant USSN10/655,861 describe either Wang et al. (PNAS 92: 8955-8959, 1995) and WO 95/29697 currently relied upon by applicant's assertions.

Upon a review of USSN 60/408,571 (e.g., see page 10, paragraph 2 - page 13), USSN 60/469,189 (e.g., see page 11, paragraph 3 - page 15) and instant USSN 10/655,861 (e.g., see page 13, paragraph 2 - page 17),

these applications have described anti-C5 antibodies generically and have described the claimed anti-C5 antibodies that inhibit the cleavage of C5 into fragments of C5a and C5b as a class of anti-C5 antibodies and as a preferred embodiment.

For example, the instant specification describes that anti-C5 antibodies that have the desirable ability to block the generation of C5a have been known in the art since 1982 (see page 14 of the specification,

and anti-C5 antibodies can bind C5 fragments thereof (e.g., C5a or C5b)

and preferably the anti-C5 antibodies are immunoreactive against epitopes of the alpha chain (and not the beta chain) of C5 and are capable of blocking the conversion of C5 into C5a and C5b by C5 convertase

and bind to amino-terminal region but not to free C5a (e.g., see page 16, paragraphs 2-3 of the specification).

In contrast to applicant's assertions of an unambiguous description that anti-C5 antibodies refers to a genus of antibodies that inhibit the cleavage of C5 into fragments of C5a and C5b, the 131 Wang Declaration and accompanying Exhibits A/B there do not describe the generic properties of anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b with particularity and with a definite and permanent idea of the compete and operative invention currently claimed and
the instant provisional and non-provisional applications describe the claimed anti-C5 antibodies that inhibit the cleavage of C5 into fragments of C5a and C5b as a class of anti-C5 antibodies and as the preferred embodiment.

In contrast to applicant's assertions, this is not an issue that applicant is free to be his own lexicographer.

The unsupported assertions of applicant's representative that it defies reason that a skilled artisan in the complement field would have believed that the inventor conceived of the therapeutic use of antibodies that do not inhibit C5 cleavage does not establish a fact.

For example, often experimental plans, publications, grant proposals and the like would provide more detailed information and specifics with sufficient guidance to understand the study with a specific settled idea, a particular solution to the problem at hand and not just a general goal or research plan, nor as limited as Exhibit A.

In contrast to applicant's assertions, the Wang 131 Declaration and accompanying Exhibits A/b do not convey with reasonable clarity to those skilled in the art that the current claimed invention.

Here, applicant's remarks rely upon unsupported assertions of what was in the mind of the skilled artisan at the time the invention was made and references (e.g., Wang et al., PNAS 92: 8955-8959, 1995 and WO 95/29697) not cited in the evidentiary record of the Wang 131 Declaration or the instant application and its priority documents.

Here, applicant's remarks are not consistent with the applicant's own disclosure that the claimed anti-C5 antibodies that inhibit the cleavage of C5 into fragments of C5a and C5b are a class of anti-C5 antibodies and a preferred embodiment and not necessarily an unambiguous meaning of anti-C5 antibodies.

The Wang 131 Declaration and accompanying Exhibits do not provide sufficient blazemarks nor direction for the instant methods encompassing the claimed limitations of anti-C5 antibodies that inhibit the cleavage of C5 into fragments of C5a and C5b are a class of anti-C5 antibodies as a preferred embodiment and not necessarily an unambiguous meaning of anti-C5 antibodies.

The instant claims now recite limitations which were not clearly disclosed in the Wang 131 Declaration and accompanying Exhibits, and changed the scope described in the Exhibits and introduce new concepts.

Obviousness is not the standard for the addition new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Here, the 131 Declaration and accompanying Exhibits A/B do not describe the claimed invention with particularity and a definite and permanent ides of the compete and operative invention prior to the provisional applications.

There is no disclosure that the generic properties of anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b in the context of the claimed invention was described in a manner that provides for conception, diligence and reduction

Applicant's arguments are not persuasive.

U.S. Provisional Patent Application No. 60/408,571: Claims 20 and 51

Applicant's arguments, filed 07/18/2011, concerning the priority of claims 20 and 51 have been fully considered but have not been found convincing essentially for the reasons of record.

In contrast to applicant's reliance upon page 4, lines 12-14 for the claimed combination therapy and the word "known" asthma therapy regimens, the instant claims recite:

Claim 20. A method for treating a subject having or susceptible to asthma comprising administering an anti-C5 antibody in combination with at least one asthma therapy regimen selected from the group consisting of steroids, anti-IgE antibodies, anti-IL-4 antibodies, anti-IL-5 antibodies, β2 adreno receptor agonists, leukotriene inhibitors, 5 Lipoxygenase inhibitors, PDE inhibitors, CD23 antagonists, IL- 13 antagonists, cytokine release inhibitors, histamine H 1 receptor antagonists, anti-histamines and histamine release inhibitors, wherein the anti-C5 antibody inhibits the conversion of complement component C5 into C5a and C5b.

Claim 51. (Currently Amended) A method as in any of claims 1-9 wherein the anti-C5 antibody is administered in combination with an asthma therapy regimen selected from the group consisting of steroids, ant-IgE antibodies, anti-IL-4 antibodies, anti-IL-5 antibodies, β2 adreno receptor agonists, leukotriene inhibitors, 5 Lipoxygenase inhibitors, PDE inhibitors, CD23 antagonists, IL-13 antagonists, cytokine release inhibitors, histamine H 1 receptor antagonists, anti\-histamines and histamine release inhibitors.

Page 4, lines 12-14 of priority USSN. 60/408,571 describes:

"[a] combination therapy may also be used that includes a complement-inhibiting compound in combination with a regimen of known asthma therapy, such as, for example, steroid, anti-IgE antibody, anti-IL-4 or anti-IL-5 antibody."

In addition, applicant relies upon the combination of anti-C5 antibody and the steroid dexamethasone in Examples 1-3 of USSN 60/408,571 as well as the description of a known asthma therapy to support the additional species recited in the instant claims.

Applicant argues that through use of the word "known", the description emphasizes that additional species of known asthma therapy regimens were in the art at the effective filing date of the application.

Applicant argues that the priority documents provides literal support for the genus of known asthma therapy regimens instantly claims, by providing literal support for at least four species embraced by that genus
and argues that upon reading the priority document, a person of ordinary skill in the art would have easily and readily understood that applicant was in possession of the claimed species.

The specification of the priority document does not provide sufficient blazemarks nor direction for the instant methods encompassing all of the currently claimed elements of the combination therapy, as acknowledged by applicant.

The instant claims now recite limitations which were not clearly disclosed in the priority document as-filed, and changed the scope of the priority disclosure as-filed.
Such limitations recited in the present claims, which did not appear in the priority document as-filed, introduced new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Also, it is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Obviousness is not the standard for the addition new limitations to the disclosure as filed.

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed.
To satisfy the written description requirement, the disclosure of the earlier filed application must describe the later claimed invention "in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought."
Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Each application in the chain leading back to the earlier application must comply with the written description requirement of 35 U.S.C. 112 and the earlier application must describe the later claimed invention in sufficient detail that one skilled in the art can clearly conclude that the invention was in possession of the claimed invention as of the filing date sought.

The hallmark of written description is disclosure.

A claim as a whole has only one effective filing date.
See Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997).

Applicant's arguments have not been found persuasive.

4. Claims 1-11, 15-18, 20-21, 45-51 and 59-60 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Krause et al. (US 2004/0014782) (see entire document) essentially for the reasons of record.

Applicant's arguments in conjunction with the Wang declaration under 37 C.F.R. § 1.131 filed 07/18/2011 have been fully considered but are not found convincing essentially for the reasons of record and herein.

Applicant's arguments and the examiner's rebuttal concerning the applicability of Krause as an anticipatory reference appear to be the same or nearly the same of record and addressed herein.

Applicant argues that eculizumab and pexelizumab are recited only twice in Krause and only in the context of "rheumatoid arthritis" and only as one of a laundry list of well known potential C5a receptor-inactive anti-arthritic agents
and that the therapeutic molecules drawn to treating lung disorders do not mention eculizumab and pexelizumab (e.g., see pages 18, 19 and 23 of Krause) versus well known asthma treatments (e.g., see paragraph [0227]-[0229] of Krause).

In turn, applicant argues that neither eculizumab nor pexelizumab are necessarily part of the expansive genus of "C5a receptor inactive agents" embraced by Krause's asthma related disclosure.

Also, applicant argues that "C5a receptor-inactive agent" imparts no structural or functional constraints on the types of compounds embraced by the genus, other than what the its members are not
and asserts that is can hardly be said the eculizumab and pexelizumab or any other anti-C5 antibodies are necessarily members of the genus of C5a receptor-inactive agents useful for treating asthma.

In addition, applicant submits that the eculizumab and pexelizumab were dissimilar from Krause's C5a receptor-inactive agents since neither antibody was well known, clinically approved or the subject of clinical trials for treating asthma or any related lung condition as the effective filing date of Krause versus those described in paragraphs [0227]-[0229] of Krause.

Again, in contrast to applicant's narrow reading of Krause et al.,

Krause et al. is clearly drawn to C5a antagonists and compositions / kits comprising said C5a antagonists and their use to treat a variety of inflammatory or autoimmune diseases / conditions (e.g., Background, Summary of the Invention and Detailed Description of the Invention, including Terminology in paragraphs [0034]-[0039]).

Again, applicant is directed to the teachings of the entire reference

In contrast to applicant's assertions,

paragraph [0207] of Krause describes anti-C5 antibodies such as eculizumab or pexelizumab, which are the same anti-C5 antibodies based upon the anti-C5 antibody 5G1.1 recited in the instant claim and encompassed by anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b.

Eculizumab is the humanized version of the anti-C5 antibody, 5G1.1

Pexelizumab is the humanized single chain version of the anti-C5 antibody, 5G1.1.

[0206] Still other embodiments of the invention are directed to combinations in which at least one C5a receptor-inactive therapeutic agent is:

[0207] an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab);

While Krause defines a C5a receptor-inactive therapeutic agent as an agent that does not satisfy the criteria set forth in paragraph [0035] for a C5a antagonist (see paragraph [0036]) and that a C5a receptor-inactive therapeutic agent can be "an active agent" (see paragraph [0037]).

[0035] A "C5a antagonist" or "C5a receptor antagonist" is any compound that exhibits C5a antagonist activity within the a C5a receptor-mediated chemotaxis, radioligand binding assay, or calcium mobilization assay as provided herein. In other words, in a calcium mobilization assay, a compound is a C5a antagonist if incubation of cells with 1 uM of C5a antagonist results in at least a 2-fold increase in the fluorescence response relative to that measured in the presence of C5a alone. In a chemotaxis assay, a compound is a C5a antagonist if it displays an affinity constant or IC.sub.50 of 1 uM or less. Preferably, a C5a antagonist displays an IC.sub.50 of less than 500 nM, 200 nM, 100 nM, 50 nM, 25 nM, 10 nM or 5 nM (in a chemotaxis and/or calcium mobilization assay) in a standard C5a receptor-mediated chemotaxis assay, radioligand binding assay, or calcium mobilization assay. In certain embodiments, C5a antagonists provided herein inhibit activation and/or activity of a primate C5a receptor, such as human C5a receptor, which may be a cloned, recombinantly expressed receptor or a naturally expressed receptor. For treating non-human animals of any particular species, a compound exhibiting high affinity for the C5a receptor of that particular species is preferred.

[0036] As used herein, "therapeutic agent" refers to a compound which has been shown to exhibit clinical efficacy in reducing the symptoms of one or more of arthritis (preferably rheumatoid arthritis) or another autoimmune disorder, asthma, cardio- or cerebrovascular disease, psoriasis, reperfusion injury, burns, or traumatic CNS or spinal cord injury. A "C5a receptor-inactive therapeutic agent" is such an agent that does not satisfy the criteria (above) for a C5a antagonist.

[0037] As used herein, "active agent" refers to either or both of the C5a antagonist and the C5a receptor-inactive therapeutic agent. This term is intended to encompass all salt, ester and prodrug forms of C5a antagonists and C5a

receptor-inactive therapeutic agents, even where the prodrug is not active itself but is converted to the active form after administration to the patient.

All three pathways of complement activation (the classical, mannan-binding lectin and alternative pathway) lead to formation of C5 convertase, which cleave C5 into C5a and C5b.

C5a is a potent anaphylatoxin that mediates leukocyte chemotaxis, increases vascular permeability, alters smooth muscle tone and induces secondary inflammatory mediators.

C5a is a key regulator of inflammation, including attracting and activation circulating cells expressing C5aR, particularly monocytes, macrophages and neutrophils.

Given that C5 is common all pathways of complement activation, blockade at this point stops the progression of the cascade regardless of the stimuli, In addition, prevention of C5 cleavage effectively blocks the generation of the potent proinflammatory molecules C5a and the cell lytic terminal complement complex (TCC).

Note, too, that C5 blockade preserves the critical immunoprotective and immunoregulatory function s of upstream components that culminate in C3b-mediated opsonization and immune complex clearance.

The prior teachings of the anti-C5 antibody 5G1.1 or its recombinant forms (eculizumab or pexelizumab) served these purposes.

That Krause may classify the anti-C5 recombinant antibodies eculizumab or pexelizumab as C5a receptors inactive therapeutic agents does not detract for their potent anti-inflammatory activities at the time the invention was made to the ordinary artisan.

That C5a receptor-inactive therapeutic agents such as anti-C5 recombinant antibodies eculizumab or pexelizumab differ from other C5a receptors inactive therapeutic agents described does not detract for these antibodies having the same functional properties and specificities described / defined by Krause (e.g., see paragraphs [0035]-[0037]) .

With respect to applicant's arguments concerning the use of anti-C5 recombinant antibodies eculizumab or pexelizumab in the treatment of asthma,
paragraphs [0279]-[0281] of Krause do describe C5a receptor antagonists and C5a receptor-inactive therapeutic agents, which, in turn, encompass anti-C5 recombinant antibodies eculizumab or pexelizumab as C5a receptors inactive therapeutic agents.

While Krause does not explicitly describe the anti-C5 recombinant antibodies eculizumab or pexelizumab in the treatment of asthma,
Krause clearly describes C5a receptor-inactive therapeutic agents, which, in turn, would encompass anti-C5 recombinant antibodies eculizumab or pexelizumab as C5a receptors inactive therapeutic agents as taught by Krause (e.g., paragraphs [0206]-[0207]).

The following is reiterated for applicant's convenience.

Krause et al. teach the use of C5a antagonists, including anti-C5 antibodies (e.g., see paragraphs [0207] and [0277]) in the treat respiratory diseases lung disorders, including ARDS and asthma (e.g., see paragraphs [0039], [0204] [0227, [0274]), including inhaled compositions, nebulizers or other devices for the treatment of asthma (e.g., see paragraphs [0273]—[0275], [0279]-[0281], [0288]-[[0303]) as well as combinations for the treatment of lung disorders (e.g., see paragraphs [0200], [0226]-[0235]) and dosages consistent with the broad range (e.g., see paragraphs [0263]-[0300]) (see entire document).

Although the reference does not disclose that all of the properties of functional or binding characteristics of antagonistic anti-C5 antibodies recited in the claims per se (e.g., reducing airway obstruction, reducing bronchial spasms, increasing airflow, inhibits the conversion of complement component C5 into C5a and C5b, etc.), it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same patient is being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Note that eculizumab or pexelizumab described in paragraphs [0207] is the same as 5G1.1, h5G1.1 or its single chain variant.

Applicant's arguments have not been found persuasive.

5. Claims 1-11, 15-18, 20-21, 45-51 and 59-60 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Krause et al. (US 2004/0014782) (1449; #AE) in view of Evans et al. (U.S. Patent No. 6,355,245), Fung et al. (U.S. Patent No. 6,956,107), Fung et al. (U.S. Patent No. 6,998,468), Lobb et al. (U.S. Patent No. 5,871,734) (1449; #AA) and the known regimens of asthma therapy, as acknowledged on page 6, paragraph 2 of the specification.

Applicant's arguments in conjunction with the Wang declaration under 37 C.F.R. § 1.131 filed 07/18/2011 have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments concerning the prior art status of Krause under 35 U.S.C. 102(e) have been fully considered but have not been found convincing essentially for the reasons set forth above in Sections 3 and 4.

Applicant's arguments and the examiner's rebuttal concerning the prior art status of Krause under 35 U.S.C. 102(e) are the same as addressed above in Sections 3 and 4.

Krause stands as 35 U.S.C. 102(e) prior art.

Applicant's arguments, rely, in part, on the experimental data of anti-C5 antibody to treat a mouse asthma model.

Applicant argues in combination with KSR and In re Young that a person of ordinary skill in not an automaton and that the ordinary artisan would have been conflicted with the role of complement component C5 in asthma.

In addition, applicant relies upon Karp et al. (Nature Immunology 1: 221-226, 2000) that there was a lower expression of C5 in severe OVA-induced inflammation in mouse lung,
and that IL-12 that was able to prevent / reverse experimental allergic asthma
to submit that Karp et al. teaches away from the notion that inhibition of C5a or C5 would be beneficial for treating asthma.

While Karp et al. notes that the identification of C5 as a susceptibility gene for experimental allergen-induced airway hyperresponsiveness in an experimental allergic asthma may have relevance to human asthma,
and shows the utility of combine genetic and genomic approaches to the analysis of complex traits in experimental rodent models (e.g., see Discussion, including page 225, column 1, paragraph 1-2);
Karp et al. reports that a direct association between C5 deficiency and airway hyperresponsivensss in the experimental remains to be fully established (e.g., see page 224, column 2, paragraph 3 in the Discussion).

Applicant also relies upon Humbles (Nature 406: 998-101, 2000) to show that a deficiency in C3a receptor alone was sufficient to show that a further teaching away from using C5 inhibitors to treat respiratory disorders such as asthma.

However, Humbles et al. also states that many features of bronchial asthma, such as smooth muscle contraction, mucus secretion and recruitment of inflammatory cells, are consistent with the actions of complement anaphylatoxins, in particular C3a and C5a (see Abstract).

Applicant argues that Krause et al. does not provide any experimental evidence that its C5a receptor antagonists are effective in treating asthma and that Krause et al. describes prophetic examples lending itself to hypothetical, conjectural and/or hoped-for results.
Here, applicant argues that Neurogen the assignee of the Krause application supported a C5a antagonist NGD-2000-1 which failed to show therapeutic benefit in patients with mild-to-moderate asthma (Exhibit E).

However, there is insufficient information to make any conclusions.

For example, given that that NGD-2000-1 was tested in humans in Phase IIa Clinical Trials,

It would be reasonable to conclude that a number of other studies, including experimental animal studies were employed prior to treatment of humans in Phase IIa Clinical Trials,

suggesting the NGD-2000-1 was tested in the same or similar experimental animal models as applicant now relies upon.

Also, the predetermined endpoints are not indicated in the Neruogen report provided.

In turn, it is not clear whether there was any measurable treatment such as ameliorating one or more symptoms associated with asthma in these human studies occurred, which was consistent with the claimed methods.

Certainly, the Phase IIa Clinical Trials would indicate that targeting C5a-C5a receptor-mediated actions were deemed to be considered potentially beneficial in the treatment of asthma, consistent with the teachings of Krause.

Again, in contrast to applicant's narrow reading of Krause et al.,

Krause et al. is clearly drawn to C5a antagonists and compositions / kits comprising said C5a antagonists and their use to treat a variety of inflammatory or autoimmune diseases / conditions (e.g., Background, Summary of the Invention and Detailed Description of the Invention, including Terminology in paragraphs [0034]-[0039]).

Again, applicant is directed to the teachings of the entire reference

In contrast to applicant's assertions,

paragraph [0207] of Krause describes anti-C5 antibodies such as eculizumab or pexelizumab, which are the same anti-C5 antibodies based upon the anti-C5 antibody 5G1.1 recited in the instant claim and encompassed by anti-C5 antibodies that inhibit the conversion of C5 into C5a and C5b.

Eculizumab is the humanized version of the anti-C5 antibody, 5G1.1

Pexelizumab is the humanized single chain version of the anti-C5 antibody, 5G1.1.

[0206] Still other embodiments of the invention are directed to combinations in which at least one C5a receptor-inactive therapeutic agent is:

[0207] an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab);

While Krause defines a C5a receptor-inactive therapeutic agent as an agent that does not satisfy the criteria set forth in paragraph [0035] for a C5a antagonist (see paragraph [0036]) and that a C5a receptor-inactive therapeutic agent can be "an active agent" (see paragraph [0037]).

[0035] A "C5a antagonist" or "C5a receptor antagonist" is any compound that exhibits C5a antagonist activity within the a C5a receptor-mediated chemotaxis, radioligand binding assay, or calcium mobilization assay as provided herein. In other words, in a calcium mobilization assay, a compound is a C5a antagonist if incubation of cells with 1 uM of C5a antagonist results in at least a 2-fold increase in the fluorescence response relative to that measured in the presence of C5a alone. In a chemotaxis assay, a compound is a C5a antagonist if it displays an affinity constant or IC.sub.50 of 1 uM or less. Preferably, a C5a antagonist displays an IC.sub.50 of less than 500 nM, 200 nM, 100 nM, 50 nM, 25 nM, 10 nM or 5 nM (in a chemotaxis and/or calcium mobilization assay) in a standard C5a receptor-mediated chemotaxis assay, radioligand binding assay, or calcium mobilization assay. In certain embodiments, C5a antagonists provided herein inhibit activation and/or activity of a primate C5a receptor, such as human C5a receptor, which may be a cloned, recombinantly expressed receptor or a naturally expressed receptor. For treating non-human animals of any particular species, a compound exhibiting high affinity for the C5a receptor of that particular species is preferred.

[0036] As used herein, "therapeutic agent" refers to a compound which has been shown to exhibit clinical efficacy in reducing the symptoms of one or more of arthritis (preferably rheumatoid arthritis) or another autoimmune disorder, asthma, cardio- or cerebrovascular disease, psoriasis, reperfusion injury, burns, or traumatic CNS or spinal cord injury. A "C5a receptor-inactive therapeutic agent" is such an agent that does not satisfy the criteria (above) for a C5a antagonist.

[0037] As used herein, "active agent" refers to either or both of the C5a antagonist and the C5a receptor-inactive therapeutic agent. This term is intended to encompass all salt, ester and prodrug forms of C5a antagonists and C5a receptor-inactive therapeutic agents, even where the prodrug is not active itself but is converted to the active form after administration to the patient.

All three pathways of complement activation (the classical, mannan-binding lectin and alternative pathway) lead to formation of C5 convertase, which cleave C5 into C5a and C5b.

C5a is a potent anaphylatoxin that mediates leukocyte chemotaxis, increases vascular permeability, alters smooth muscle tone and induces secondary inflammatory mediators.

C5a is a key regulator of inflammation, including attracting and activation circulating cells expressing C5aR, particularly monocytes, macrophages and neutrophils.

Given that C5 is common all pathways of complement activation, blockade at this point stops the progression of the cascade regardless of the stimuli, In addition, prevention of C5 cleavage effectively blocks the generation of the potent proinflammatory molecules C5a and the cell lytic terminal complement complex (TCC).

Note, too, that C5 blockade preserves the critical immunoprotective and immunoregulatory function s of upstream components that culminate in C3b-mediated opsonization and immune complex clearance.

The prior teachings of the anti-C5 antibody 5G1.1 or its recombinant forms (eculizumab or pexelizumab) served these purposes.

That Krause may classify the anti-C5 recombinant antibodies eculizumab or pexelizumab as C5a receptors inactive therapeutic agents does not detract for their potent anti-inflammatory activities at the time the invention was made to the ordinary artisan.

That C5a receptor-inactive therapeutic agents such as anti-C5 recombinant antibodies eculizumab or pexelizumab differ from other C5a receptors inactive therapeutic agents described does not detract for these antibodies having the same functional properties and specificities described / defined by Krause (e.g., see paragraphs [0035]-[0037]) .

With respect to applicant's arguments concerning the use of anti-C5 recombinant antibodies eculizumab or pexelizumab in the treatment of asthma,

paragraphs [0279]-[0281] of Krause do describe C5a receptor antagonists and C5a receptor-inactive therapeutic agents, which, in turn, encompass anti-C5 recombinant antibodies eculizumab or pexelizumab as C5a receptors inactive therapeutic agents.

While Krause does not explicitly describe the anti-C5 recombinant antibodies eculizumab or pexelizumab in the treatment of asthma,

Krause clearly describes C5a receptor-inactive therapeutic agents, which, in turn, would encompass anti-C5 recombinant antibodies eculizumab or pexelizumab as C5a receptors inactive therapeutic agents as taught by Krause (e.g., paragraphs [0206]-[0207]).

Applicant asserts that the secondary reference do not cure the deficiencies of Krause et al.

Applicant argues that both Fung et al. references direct one to either anti-Factor D antibodies and anti-C2a antibodies, which are directed to acting upon the C3 convertase step of complement and do not provide for inhibiting C5 is therapeutically useful as claimed.

Although it has been acknowledged that Fung et al. (U.S. Patent No. 6,956,107) was focused on Factor D inhibitors,

Fung et al. teach the role of C5a anaphylatoxin in complement-mediated inflammation (e.g., see Background of the Invention), including the inhibition of C5a anaphylatoxin (e.g., see column 9, lines 39-41) in the context of severe asthma (e.g., see column 9, lines 62-63) as well as appropriate pharmaceutical formulations that can be administered by a variety of routes, including intranasal and intratracheal (e.g., see column 9, lines 32-38).

Although it has been acknowledged that Fung et al. (U.S. Patent No. 6,998,468) was focused on complement Ca2 inhibitors,

Fung et al. teach the role of C5a anaphylatoxin in complement-mediated inflammation and the inhibition of the complement and lectin complement pathways including C5 convertases and C5 activation (e.g., see Background of the Invention and Applications of the Anti-C2a Molecules).

Applicant's assertions do not take place of the evidence in the record of inhibition of C5a in the context of severe asthma as taught by Krause et al., Fung et al. (U.S. Patent No. 6,956,107) and Fung et al. (U.S. Patent No. 6,998,468).

Applicant submits that the secondary references Evans and Lobb do not remedy the deficiencies of the primary reference.

The teachings of Evans directed to anti-C5a antibodies, including the 5G1.1 specificity, and Lobb directed to combination therapy in the context of asthma are of record and reiterated herein.

In response to applicant's arguments that there is no suggestion to combine the references including reliance upon KSR, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981).

One cannot show non-obviousness by merely asserting that the references do not provide the sufficient elements of obviousness or by attacking references individually where the rejections are based on a combination of references. In re Young, 150 USPQ 725 (CCPA 1968).

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (e.g., targeting C5/C5 receptor in the treatment of asthma and anti-C5 antibodies, including the 5G1.1 specificity and advantages thereof, in the treatment of inflammatory diseases) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (administering anti-C5 antibodies) to target inflammatory conditions of interest (e.g., asthma) with no change in their respective functions and the combination would have yielded nothing more than predictable results of treating asthma with anti-C5 antibodies.

The rationale to support a conclusion that the claims would have been obvious is that a method of targeting C5/C5 receptor in the treatment of asthma as well as the applicability of anti-C5 antibodies, including the 5G1.1 specificity and advantages thereof, in the treatment of inflammatory diseases was made part of ordinary capabilities of one skilled in the art based upon the teachings of the prior art. One of ordinary skill in the art would have been capable of applying the known anti-C5 antibodies, including the 5G1.1 specificity and advantages thereof, in the treatment of inflammatory diseases in the treatment of asthma and would have been predictable to one of ordinary skill in the art at the time the invention was made.

The rationale to support a conclusion that the claims would have been obvious is that a particular known technique (anti-C5 antibodies, including the 5G1.1 specificity and advantages thereof, in the treatment of inflammatory diseases and targeting C5/C5 receptor in the treatment of asthma) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying these known techniques to a target asthma that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g., targeting C5/C5 receptor in the treatment of asthma and the applicability of anti-C5 antibodies, including the 5G1.1 specificity and advantages thereof, in the treatment of inflammatory diseases) within his or her technical grasp. This leads to the anticipated success of treating asthma with anti-C5 antibodies, including the 5G1.1 antibody. It is likely the product not of innovation but of ordinary skill and common sense.

Since treating asthma with C5 antagonists and treating inflammatory diseases with anti-C5 antibodies, including the 5G1.1. specificity, would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of an treating asthma with anti-C5 antibodies. The prior art had recognized the advantages of targeting C5 in the treatment of asthma and targeting inflammatory conditions with anti-C5 antibodies to accomplish such goals. The claims were obvious because it would have been obvious to try to treat asthma with anti-C5 antibodies with a reasonable expectation of success.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to treat asthma with C5/C5 receptor antagonists, incorporating known anti-C5 antibodies, including the 5G1.1 specificity, that served to treat inflammatory conditions, would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing therapeutic regimens, including combination therapies, to treat asthma.

The following is reiterated for applicant's convenience.

Krause et al. teach the use of C5a antagonists, including anti-C5 antibodies (e.g., see paragraphs [0207] and [0277]) in the treat respiratory diseases lung disorders, including ARDS and asthma (e.g., see paragraphs [0039], [0204] [0227, [0274]), including compositions for the treatment of asthma (e.g., see paragraphs [0273]—[0275], [0279]-[0281], [0288]-[[0303]) and instructions (e.g., see claim 29, paragraphs 263, [0273], [0278], [0297]) as well as combinations for the treatment of lung disorders (e.g., see paragraphs [0200], [0226]-[0235]) and dosages consistent with the broad range recited in claim 31 (e.g., see paragraphs [0263]-[0300]) (see entire document).

Although the reference does not disclose that all of the properties of functional or binding characteristics of antagonistic anti-C5 antibodies recited in the claims per se (e.g., reducing airway obstruction, reducing bronchial spasms, increasing airflow, inhibits the conversion of complement component C5 into C5a and C5b, etc.), it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Furthermore, the functional or binding characteristics of antagonistic anti-C5 antibodies recited in the claims (e.g., reducing airway obstruction, reducing bronchial spasms, increasing airflow, inhibits the conversion of complement component C5 into C5a and C5b, etc.) in the treatment of asthma or other pulmonary inflammatory conditions would have been obvious therapeutic endpoints in view of the teachings of the therapeutic utilities of the antagonistic anti-C5 antibodies taught by Krause et al., as these therapeutic endpoints would have been obvious therapeutic endpoints in the amelioration or treatment of said inflammatory pulmonary conditions.

Although Fung et al. (U.S. Patent No. 6,956,107) was focused on Factor D inhibitors, Fung et al. teach the role of C5a anaphylatoxin in complement-mediated inflammation (e.g., see Background of the Invention), including the inhibition of C5a anaphylatoxin (e.g., see column 9, lines 39-41) in the context of severe asthma (e.g., see column 9, lines 62-63) as well as appropriate pharmaceutical formulations that can be administered by a variety of routes, including intranasal and intratracheal (e.g., see column 9, lines 32-38).

Although Fung et al. (U.S. Patent No. 6,998,468) was focused on complement Ca2 inhibitors, Fung et al. teach the role of C5a anaphylatoxin in complement-mediated inflammation and the inhibition of the complement and lectin complement pathways including C5 convertases and C5 activation (e.g., see Background of the Invention and Applications of the Anti-C2a Molecules).

In addition, Evans et al. provides for a more complete teachings of making and using 5G1.1 anti-C5 antibody in inhibiting inflammation, including the binding and functional characteristics recited in claims 12-16) (see entire document).

Note that eculizumab or pexelizumab described in paragraphs [0207] is the same as 5G1.1, h5G1.1.

In addition, page 6, paragraph 2 of the instant specification acknowledges the known reagents employed in asthma regimens.

Given the teachings of combination therapy by Krause et al., it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ antagonistic anti-C5 antibodies in combination with the known regiments either taught by Krause et al. or as acknowledged by page 6, paragraph 2 of the instant specification as equivalents or obvious substitutions regularly practiced by the ordinary artisan at the time the invention was made.

In addition to the teachings above, Lobb et al. teach that aqueous antibody solutions can be delivered to airways using a nebulizer (e.g., see column 6, lines 36-41 and column 12, lines 37-52) as well as the use of antibodies for the treatment of asthma (see entire document, including Summary of the Invention). Note, too, that Lobb et al. also teach the well known applicability of combination therapy, including combination having a therapeutic effect on airway responsiveness (e.g., see column 8, paragraphs 4-5).

On this record, it is reasonable to conclude that the same patients are being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art reference

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to employ combination therapy with anti-C5a antibodies in the treatment of certain respiratory / lung disorders / diseases such as asthma One would have been motivated with a reasonable expectation of success to administer the antibodies directly to the respiratory mucosa, which is often the first line of encounter of an immune system with pathogenic organisms and by the teachings of the prior art as a known and effective means to target the respiratory system in the treatment of certain disorders/diseases.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to inhibit complement activation in order to treat pulmonary diseases/conditions, incorporating known inhibitors such as anti-C5 antibodies into therapeutic regiments to treat inflammatory lung / pulmonary conditions such as asthma would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing therapeutic regimens to treat such inflammatory pulmonary diseases / conditions.

From the teachings of the references, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

6. Claims 1-11, 15-18, 20-21, 45-51 and 59-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31-34, 38-45 and 48 of copending USSN 11/127,438 for the reasons of record.

The instant and copending claims are drawn to the same or nearly the same methods of treating pulmonary conditions such as asthma with the same anti-C5 antibodies. Combination therapy in the treatment of various conditions, including pulmonary conditions / asthma were well known in the prior art at the time the invention was made.

The instant and copending claims either anticipate or render obvious one another.

Applicant's remarks, filed 07/18/2011, assert that pursuant to MPEP 804 that the instant filed application is the earlier filed application and that the provisional rejection will be the only remaining rejection after applicant's arguments are sustained.

In turn, applicant requests that the provisional rejection be withdrawn and to allow the case to issue without a terminal disclaimer.

In contrast to applicant's assertions, the prior art rejections as well as the provision double patenting rejections are sustained.

Also, note that the instant and copending USSNs have the same filing date for the purposes of double patenting, as the filing date is measured from the filing date of the earliest filed application whose benefit is claimed under 120, 121 or 365(c).

In this case, both the instant and copending USSNs have the same priority date.

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
October 11, 2011